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# Development of core outcome sets for people undergoing major lower limb amputation for complications of peripheral vascular disease

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## Abstract

### Background

Every year, thousands of patients with peripheral vascular disease undergo major lower limb amputation. Despite this, evidence for optimal management is weak. Core outcome sets capture consensus on the most important outcomes for a patient group to improve the consistency and quality of research. We aimed to define short- and medium-term core outcomes sets for studies involving patients undergoing major lower limb amputation

### Methods

A systematic review of the literature; and focus groups involving patients, carers and healthcare professionals; were used to derive a list of potential outcomes. Findings informed a three-round online Delphi consensus process, where outcomes were rated for both short-term and medium-term studies. Results of the Delphi were discussed at a face-to-face consensus meeting, and recommendations made for each core outcome set.

### Results

A systematic review revealed 45 themes to carry forward to the consensus survey. These were supplemented by a further five from focus groups. The consensus survey received responses from 123 participants in round 1, and 91 individuals completed all three rounds. In the final round, nine outcomes were rated as 'core' for short-term studies and a further nine for medium-term studies. Wound infection and healing were rated as 'core' for both short-term and medium-term studies. Outcomes related to mortality, quality of life, communication and additional healthcare needs were

also rated as 'core' for short-term studies. In medium-term studies, outcomes related to quality of life, mobility and social integration/independence were rated as 'core'. The face-to-face stakeholder meeting ratified inclusion of all outcomes from the Delphi and suggested that deterioration of the other leg and psychological morbidity should also be reported for both short- and medium-term studies.

## Conclusions

We established consensus on 11 core outcomes for short- and medium-term studies. We recommend that all future studies involving patients undergoing major lower limb amputation should report these outcomes.

## What does this study add to the existing literature and how will it influence future clinical practice?

Major lower limb amputation is a common procedure, but evidence for optimal management is weak and the literature is heterogeneous. Through a rigorous four-step process we have established consensus on core outcome sets for this patient group, identifying 11 core outcomes each for short- and medium-term studies involving patients undergoing major lower limb amputation. Adoption of these core sets will improve the consistency and quality of research and audit for this patient group.

## Introduction

Levels of lower limb peripheral vascular disease are rising globally, with rates exceeding 10% of the population in those aged 65-69 years.<sup>1</sup> Despite advances in techniques for revascularisation, a small but significant proportion (1-2%) of these patients progress to non-reconstructable or non-salvageable peripheral vascular disease, and ultimately to major lower limb amputation (MLLA).<sup>2</sup> This has led to high numbers of MLLA throughout the world, with rates of between 7 and 40 per 100,000 population in a recent worldwide study.<sup>3</sup>

Poor outcomes after MLLA in the UK have been highlighted by a report from the National Confidential Enquiry into Patient Outcome and Death (NCEPOD).<sup>2</sup> This showed a 12.4% 30-day mortality rate, with more than 30% of patients dying in hospital within 90 days. This was worse than most of Europe and the USA. Major problems highlighted included poor peri-operative pain control and peri-operative complication rates as a result of comorbid cardiovascular and respiratory disease. In light of these poor outcomes, it is important to define what the most important outcomes are from the perspective of patients, carers and healthcare professionals, so that quality improvement and research might be targeted at the most important problems.

'Core outcome sets' have been developed in many clinical areas.<sup>4</sup> Core outcome sets aim to establish consensus on which key outcomes should be reported for all studies involving a particular group of patients, thereby representing a minimum standard. This is somewhat similar to, but different from reporting standards,<sup>5,6</sup> which are concerned with harmonising pre-existing items reported in registries and trials. To generate a core outcome set, patients and professionals are asked what the most important outcomes are to them. There is no assessment of how these items are measured in practice. As a result, core outcome sets sometimes include outcomes which we

have no good way of measuring. Reporting standards are generated to harmonise reporting between pre-existing items in registries, so the lists of outcomes within them are likely to be somewhat different to those found in a core outcome set for the same condition. If core outcome sets are adopted, future research will then be better targeted, and different interventional studies and observational registries will also be more directly comparable, facilitating meta-analysis. Improving the efficiency of research is also likely to have significant knock-on quality improvement benefits. Core outcome sets have now been published for conditions as diverse as Rheumatoid Arthritis and Head and Neck Cancer,<sup>7,8</sup> with 1300 projects registered with the initiative up to December 2019, but as yet there are no core outcome sets for any conditions treated by Vascular Surgeons.

The aim of this project was to develop core outcome sets for studies or registries reporting on patients undergoing MLLA as a consequence of peripheral vascular disease. During development of this project, it became apparent that core outcomes for patients undergoing MLLA might vary depending on whether a study was focussed on short-term or longer-term outcomes. We therefore aimed to develop two separate but complementary core outcome sets: one for short-term studies, defined as up to 30 days or before hospital discharge; and one for medium-term studies, covering periods up to two years after MLLA. A fuller explanation of the reasons for this decision is given in the published protocol.<sup>9</sup>

## Methods

The process of generating a core outcome set is described in *The COMET Handbook*.<sup>10</sup> We followed the COS-STAR checklist for reporting.<sup>11</sup>

Briefly, the process begins with the creation of a long-list of outcomes, using both a systematic review of the literature and also focus groups with a range of stakeholders to ensure that the outcomes which have been reported in previous studies capture the full extent of problems facing this patient cohort. This long-list is then reduced to a shorter list of domains, where similar outcomes are grouped together, and this reduced list is then used as the basis for a 2-3 round Delphi consensus survey, followed by a face-to-face meeting. The study protocol has been published,<sup>9</sup> so we describe the methods only briefly here. The study was granted ethical approval by Wales REC 3 (reference number 16/WA/0353) and prospectively registered with the COMET initiative (<http://www.comet-initiative.org/studies/details/975>).

### Phase I: Systematic review

The systematic review process which underpins core outcome set development differs from the standard approach to systematic review as the goal of the process is different. Systematic review standards do, however, provide a useful framework for the process, so where applicable we followed the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) framework.<sup>12</sup> The review was prospectively registered in the PROSPERO registry (ID: CRD42017059329).



### Criteria for considering studies

All clinical studies reporting at least one short- (within 30 days) or medium-term (up to 2 years) outcome involving human subjects undergoing MLLA (i.e. amputation of the lower limb above the ankle) as a result of peripheral vascular disease were included. Studies reporting only patients undergoing amputation for non-ischaemic disease such as trauma, tumour, chronic non-ischaemic pain or congenital malformations were excluded. Cross-sectional studies recruiting established patients who had had an amputation some time in the past were also excluded. Non-English language clinical studies were included if there was a publicly available translation of either the abstract or full study, although data extraction were limited to what was available in the English language.

### Outcomes

All outcomes described as either primary or secondary outcomes from included studies are reported. When more than a single study reported an outcome, the number and proportion of studies reporting that outcome were reported.

### Search strategy

MEDLINE and EMBASE were searched through Ovid using the MeSH terms given in Supplementary Table 1. Titles and abstracts were screened by two authors independently (GKA and NV).

Disagreements were resolved through discussion and consensus with a generally inclusive policy and arbitration by the senior author if necessary. Since the aim of the review was to identify all reported outcomes, inclusion of borderline studies was felt to be preferable, based on the premise that non-relevant outcomes were likely to be removed by the consensus process.

## Data extraction

A standardised data collection proforma was used. Outcome measures were extracted verbatim where possible. Studies involving patients undergoing MLLA for indications other than peripheral vascular disease were excluded. As this study focuses on which outcomes are reported rather than the value of those outcomes, neither study quality nor risk of bias was relevant, so were not assessed. Outcome measures were extracted by two independent reviewers (GKA and JARJ) for the first 20% of studies, after which concordance of extraction was checked according to the method set out in the protocol,<sup>9</sup> with 'good' concordance enabling independent extraction for the remainder.

## Results synthesis

We sought to reduce the long-list of all outcome measures to a manageable list of discrete domains, for subsequent rating in a Delphi survey of their relative importance. This was done using the system developed by Dodd et al. who classify outcomes into five main areas, subdivided into a total of 38 domains.<sup>13</sup> The outcome measures were thus reduced to a set of outcome domains: for example mortality at different time points and survival measures were grouped together into the single outcome 'death within a specified period of time after operation, or survival after the operation'. The results of the domain short-listing were discussed at study management group meetings where trials managers, statisticians, qualitative researchers, vascular surgeons and lay representatives were present.

## Phase II: Qualitative focus groups

Following discussions with qualitative researchers and others with prior core outcome set experience, participants were divided into three groups: patients and carers; nurses and allied healthcare professionals; and medically trained professionals. This was to allow everyone's voice to be heard equally and for people to feel they could express themselves fully. Participants in the two healthcare professional groups were allowed to cross over into the other group, if necessary, to improve participation, and separate interviews were held if an invitee was unable to attend any of the group sessions. We performed purposive sampling of patients to invite a broad group of people with amputations. Full details of the focus group methodology can be found in the protocol.<sup>9</sup>

Themes discussed and developed in the focus groups were translated into research outcomes similar to those from the systematic review. These were then matched to identify unique outcomes not found in the results of the systematic review, and the lists combined.

## Phase III: Delphi survey

Following synthesis of results from the systematic review and qualitative focus groups, stakeholders (patients, carers and health and social care workers) were surveyed to determine which outcomes should comprise the short- and medium-term core outcome sets for studies of MLLA for peripheral vascular disease. All individuals who participated in focus groups were invited to take part in the Delphi survey, as were all patients recruited in a concurrently running randomised trial (the PLACEMENT trial),<sup>14</sup> who had agreed to be contacted for this purpose. Several other patients with amputations were also invited. Patients were also encouraged to ask their carers to participate. In addition, the survey was advertised via multiple national and international groups including the

Vascular Society of Great Britain and Ireland, the British Society for Endovascular Therapy, the European Society for Vascular Surgery Vascunet collaboration, the British Association of Chartered Physiotherapists in Amputee Rehabilitation, the Douglas Bader foundation and Blesma (the limbless veterans charity).

The survey was a three-round Delphi consensus process,<sup>15</sup> and used the DelphiManager software from Liverpool University, supplemented with paper surveys for patients who said that they would prefer to complete a paper survey. Stakeholders were asked to rate putative outcomes on a 1-9 Likert-like scale, with 7-9 labelled as 'essential' (must be reported in all studies), 4-6 as 'desirable', and 1-3 as 'not important', with low scoring outcomes removed between rounds and participants given the opportunity to suggest additional outcomes at the end of round 1, which were incorporated into subsequent rounds. The criteria used for retaining outcomes between rounds and final acceptance in round 3 are described in the protocol.<sup>9</sup> In rounds 2 and 3, participants were given graphical feedback on how other panel members had rated each outcome in the previous round, and reminded what rating they had given in the previous round. A draft of the survey was tested by four lay people and five healthcare professionals to examine face validity, comprehension and acceptability and feedback from this was incorporated into the final version of the survey.

#### Phase IV: Synthesis of results and nominal group analysis

The results of the consensus survey were discussed at a face-to-face meeting of key stakeholders to determine final lists of short-term and medium-term outcomes which would represent the core outcome sets. Stakeholders included members of the PLACEMENT Trial Management Group, along with individuals from professions or specialties not represented by the Group, who participated in the focus groups in phase II. Participants from all professional stakeholder groups agreed to attend

the meeting. We invited eight patients who had had major lower limb amputations as previous experience had led us to believe that it would be difficult for many of these patients, who are often frail with limited mobility, to attend. Five patients and one carer agreed to attend.

Members of the face-to-face meeting were all given the opportunity to comment on the results of the Delphi survey and suggest solutions to any perceived problems which might arise with the Delphi survey results, before voting on inclusion or exclusion of proposed outcomes.<sup>9</sup>

## Results

### Phase I: Systematic Review

#### Results of the search

MEDLINE and EMBASE were searched on 20<sup>th</sup> April 2017 using the search protocol detailed in Supplementary Table 1. The search revealed 4288 studies after removal of duplicates, with a further 153 studies identified by screening reference lists. After title and abstract screening, 500 full texts were reviewed and 440 studies were included in qualitative synthesis. A flow chart based on the principles of PRISMA is shown in Supplementary Figure 1.

#### Excluded and Included studies

Studies from 42 different countries were included (Figure 1). These came most frequently from the USA (167 studies) or the United Kingdom (79 studies). Supplementary Table 2 gives a complete breakdown of the number of studies included from each country. This included 16 case reports, 292 retrospective case series or cohort studies, 100 prospective cohort studies, two studies which included both prospective and retrospective cohorts, nine non-randomised controlled trials, 20 randomised controlled trials and one qualitative study. The median number of patients included in the studies was 84 (range 1-186,338). In the 73.4% of the studies reporting patients' gender, the proportion of male patients was 61.2%. Mean or median age of participants was reported in 418 studies (95%), the overall weighted mean age being 73.5 years (range 34-93.5 years).

## Extraction of reported outcomes

There were 1447 outcome measures reported by the 440 included papers (average 3.29 outcomes per study), of which 444 were distinct outcome measures. The most frequently reported outcomes were 'mortality' and 'wound healing', each reported in 93 studies. There were 281 distinct outcomes reported only by single studies. All outcomes were grouped into domains.<sup>13</sup> There was considerable overlap across the 444 outcomes reported in the literature and we reduced this to 48 outcomes which were measuring distinct concepts, three of which were felt not to be relevant to a core outcome set for patients undergoing MLLA for complications of peripheral vascular disease. A complete list of the outcomes reported, along with the frequency of reporting, is given in Supplementary Table 3.

## Phase II: Qualitative focus groups

The focus groups took place on 15<sup>th</sup> September (mixed healthcare professionals; group 1), 28<sup>th</sup> September (patients and carers; group 2) and 6<sup>th</sup> October 2017 (doctors; group 3). A further interview with two physiotherapists specialising in the care and rehabilitation of patients who have had major limb amputation took place on 1<sup>st</sup> December 2017 (group 4), as neither of the invited physiotherapists could attend the previous focus groups.

A list of the professions/specialties invited, along with those who agreed to attend and those who attended is given in Table 1. One non-medically trained healthcare professional (a clinical psychologist) attended the focus group intended for medically trained healthcare professionals.

Five patients and five carers agreed to participate, of which three patients and three carers attended. Of the three patients who attended, one (female) had a unilateral below knee

amputation, one (male) had bilateral below knee amputations and one (male) had one below knee and one above knee amputation. The three carers who attended all cared for people with above knee amputation, none of whom attended the focus group. In addition to the patients and carers whose invitations are noted above, we also invited one individual who was known to the study team owing to her participation as lay representative on the PLACEMENT trial monitoring group, whose father had undergone amputation.

### Thematic framework

The full thematic framework is presented in Supplementary Table 4. Nineteen main themes were identified. Most themes mapped to outcomes which were already found in the systematic review, however there were five themes that were not adequately captured by these outcomes, including: the impact of amputation on family or loved ones; shared decision-making; effective communication between healthcare team and patient/carers; use of drugs or therapies which have not been prescribed; and the number of outpatient appointments.

### Delphi survey

The Delphi Survey commenced in August 2018 and round 3 was completed in December 2018.

There were 123 participants who completed round 1, and 91 (74%) completed all three rounds.

The Delphi panel comprised patients/carers, occupational therapists, physiotherapists, prosthetists, nurses, vascular surgeons, diabetologists, and clinical psychologists. Details of the participants in the three Delphi rounds, and the number of outcomes rated in different rounds are given in Figure 2. Of the 27 outcomes rated in the final round of the Delphi survey, 18 received high enough support to be considered 'core' according to the protocol:<sup>9</sup> nine for studies with a short-term focus



and nine for studies with a medium-term focus. The distribution of ratings for the short- and medium-term outcomes rated as 'core' by the Delphi survey are shown in Supplementary Figures 2 and 3 respectively, and the average ratings are given in Supplementary Tables 5 and 6.

### Face-to-face consensus meeting

The final part of the core outcome sets development project was a face-to-face meeting to discuss the results of the Delphi survey and to make the final recommendations for inclusion of outcomes. The meeting took place on Friday, April 12<sup>th</sup>, 2019 in Cardiff. Full details of the make-up of the consensus panel are given in Supplementary Table 7.

The panel recommended to accept all of the outcomes in each of the short-term and medium-term sets – unanimously in the case of all but one of the outcomes. After much discussion, two participants voted to remove 'Effective communication between healthcare team and patient/carers' from the short-term core outcome set, with nine disagreeing. In the medium-term set, after discussion it was proposed that the outcome 'Pain in residual limb/amputation stump' be changed to 'Pain in residual limb/amputation stump/phantom', to include the phenomenon of phantom limb pain. This received unanimous support when voted upon.

There was also much discussion about psychological morbidity and the importance of deterioration of the contralateral limb. Addition of these outcomes to both short- and medium-term core outcome sets was supported by over 75% of the panel, the threshold used in the third round of the Delphi.

## Final core outcome sets

The final core outcome sets (with Delphi participants' scores) for studies focusing on short-term (<30 days) and medium-term outcomes (30 days to 2 years) are shown in Figures 3 and 4 respectively. The outcomes have been grouped informally together with similar constructs in these Figures in order to provide a way of graphically summarising the results. They should not be confused with the 'domains' used to formally group outcomes together within the Delphi survey.

## Discussion

We developed short-term and medium-term core outcome sets for studies recruiting patients undergoing MLLA for complications of peripheral vascular disease. Four outcomes are shared between both short-term and medium-term sets, while the remaining seven outcomes in each set were felt to be 'core' for only one time period.

To our knowledge, this is the first time that core outcome sets for studies of patients with the same condition but for different durations have been developed. Broad ranges of outcomes are present in both short- and medium-term sets, including local stump-related problems (healing, infection, pain); further health and healthcare (readmissions, re-operations, complications, problems with the other leg); psychosocial problems (psychological morbidity, work/social re-integration, communication); mobility, independence and quality-of-life. There are objective 'hard' outcomes such as mortality, which are easily captured in routinely collected data, but there are also multiple outcomes which require patient-reported outcome measurement (PROM) instruments. To our knowledge there are no PROM tools that holistically capture mobility, pain, anxiety and depression in patients after MLLA.

No other work has defined core outcome sets for patients undergoing MLLA, although there has been some work using the International Classification of Functioning, Disability and Health to classify factors influencing mobility in patients who had a major lower limb amputation some time ago and have achieved a stable level of function.<sup>16</sup> While not a true core outcome set, this work did like ours find that problems of pain, mobility, functional independence and participation in work and social activities were important for these patients.

A strength of our work is that we had input from patient and carer representatives throughout the work. A patient and a carer on the study team reviewed all patient-facing material including information leaflets and the Delphi survey to ensure that wording was in plain English. We also used focus groups of patients, carers and healthcare professionals to ensure that outcomes important to individuals who would be unlikely to contribute to the research literature were also considered. This was important, as we added five outcomes from the focus groups, two of which made it to the final consensus survey round , and one (effective communication between healthcare team and patient/carers) is part of the final core outcome sets, described by one of the patients as the most important outcome in the short-term set. There are other examples where during the development of core outcome sets it was discovered that outcomes which are viewed as important by patients or their informal carers had not been given consideration in the scientific literature, as research is dominated by clinical practitioners, highlighting the importance of this step.<sup>17</sup> Conversely, it is possible that healthcare professionals identify outcomes which patients are hesitant to discuss and which, because of perceived difficulties in recruitment for such studies, are also not well represented in the literature.<sup>18</sup>

A further strength of the work is the way in which feedback was given to participants graphically between rounds, showing the ratings that other participants had given each outcome. Feedback between rounds of a Delphi process is essential for establishing consensus by informing participants how their peers have rated items in previous rounds.<sup>10</sup> The optimal way to do this is an active area of research, but one recent small study found that patients participating in a Delphi had a poor understanding of numerical summaries (mean, median), and a better understanding of both pie chart and histogram-style feedback.<sup>19</sup> The majority preferred histogram-style feedback, which is consistent with the method used here.

A weakness of the study is the small number of patients and carers who participated in the consensus survey or face-to-face meeting. This was despite contacting scheduled participants in the few days before the meeting to remind them and arrange transportation. This has been our experience in other research with patients undergoing amputation and is very difficult to overcome.<sup>14</sup> It is unlikely that this can be improved, but we acknowledge that a relatively low number of patients undergoing amputation may mean we have missed outcomes important to patients with amputations who are unable to get out of their living environment to attend such a meeting.

A further limitation is in terms of the composition of the professionals on the Delphi panel. This was clearly a self-selecting group, as it was composed of those who responded to our requests for contributions. This is a weakness with any Delphi process. We cannot therefore be sure that those who were not interested in taking part in the process would not have had different opinions to those who chose to take part. We attempted to mitigate against an imbalance in the distribution of opinions in the Delphi by ensuring that a broad range of stakeholders from different professions took part in the face-to-face meeting. Indeed, as a result of this meeting, some outcomes which had not quite met the criteria for inclusion on the basis of the Delphi results were also included in the final core sets. Use of a face-to-face meeting in this way following the Delphi survey is a standard part of core outcome set development, as set out in the COMET handbook.<sup>10</sup> A further limitation is that 26% of those participating in round 1 of the Delphi failed to complete all three rounds. Survey rounds required rating a significant number of potential outcomes (100 in round 1, 90 in round 2 and 27 in round 3) so it is likely that drop-out related to this high number. A recent study looking at factors associated with drop-out rates in Delphi surveys found response rates between 45% and 93% for panels with at least 100 members, with high response rates associated

almost exclusively with surveys where fewer than 50 outcomes were rated.<sup>20</sup> In this context, we feel that our response rate of 76% is good.

The development of core outcome sets represents an important step forward in improving the efficiency of further research. Results of the systematic review highlighted the inefficiency of previous research in this area, with 444 different outcomes reported in the 440 included studies. This was despite doing our best to only merge outcomes with different labels for the same measure (resulting in a reduction from 1447 to 444 outcomes). Having established consensus on the most important outcomes for these patients, future research can be more focused, and will make meta-analysis more feasible.

Core outcome sets also have the potential to improve the quality of observational research in the form of registry studies. If national registries adopt the outcome sets then results from different registries may be pooled, improving the power of such analyses. Standardisation will also be possible, allowing appropriate correction at scale for confounding factors to be performed in a uniform way across multiple registries. Work has already begun in this direction in vascular surgery, though not for patients undergoing amputation.<sup>21</sup>

While this potential is exciting, core outcome sets must be adopted before this potential can be realised. This can be a slow process, but experience from early adopters of core outcome sets is encouraging. The core outcome set for rheumatoid arthritis was one of the first published core outcome sets.<sup>7</sup> Twenty years after its publication, the vast majority of interventional studies in rheumatoid arthritis were reporting the entire core set.<sup>22</sup> In the modern era, where information passes swiftly via social media platforms such as Twitter, and journal articles are available online

and can be viewed on the go with a smartphone, we are optimistic that adoption of methodological advances such as core outcome sets should be more rapid than it has been historically.

We have developed core outcome sets for short- and medium-term studies recruiting patients undergoing major lower limb amputation. Further work is required to explore how best to measure these outcomes, using the standard approaches set out by the COSMIN initiative.<sup>23</sup> Development and validation of patient-reported outcome measurement tools which capture outcomes such as pain, communication, mobility, psychological morbidity and quality-of-life will be an important part of this. Core outcome sets are ultimately only useful if they are widely adopted, so it is essential that future studies adopt – and that funding bodies require researchers to focus on – these core outcomes.

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## Figure captions

Figure 1: Country of origin of studies included in the systematic review.

Figure 2: Flow diagram of participation in the Delphi survey.

Figure 3: Final short-term core outcome set.

Figure 4: Final medium-term core outcome set.